Docket No. 25401-24

PATENT

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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicant:	Ib Mendel-Hartvig et al	:	Paper No.:
Serial No.:	09/582,741	:	Group Art Unit: 1641
Filing Date:	October 6, 2000	:	Examiner: G. Counts

For: **Method Using a New Calibrator and a Device and Test Kit Including the Calibrator**

APPEAL BRIEF

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The present Appeal Brief is submitted in support of the Notice of Appeal filed by Certificate of Mail on July 6, 2004 and received by the U.S. Patent and Trademark Office on July 12, 2004.

I. REAL PARTY IN INTEREST

The real party in interest in this appeal is the assignee of the present application, Pharmacia Diagnostics AB.

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to the Appellants, the Appellants' undersigned legal representative or the assignee which will directly effect or be directly

effected by or having a bearing on the Board's decision in the present appeal. However, the Board may consider copending appeals in Applications Serial Nos. 09/582,808 and 09/582,734 to be of interest.

III. STATUS OF THE CLAIMS

As set forth below, it is believed that claims 1-4, 6, 11-32 and 34-39 are pending in this application and stand rejected. Claims 5, 7-10, 27 and 33 are believed to be cancelled. A copy of the claims on appeal is set forth in the Appendix.

IV. STATUS OF AMENDMENT FILED SUBSEQUENT TO REJECTION ON APPEAL

An Amendment Under 37 C.F.R. §1.116 was filed by certificate of mailing on July 6, 2004, amending claim 1 to include the limitation of claim 33 and amending claim 11 to correspond with claim 1. It is not clear to Appellants if the Amendment has been entered or has been refused entry. In the Advisory Action dated August 9, 2004, there was no indication in box 2 that the Amendment would not be entered nor was there any reason given for not entering the Amendment. On the other hand, box 7 indicated the Amendment would not be entered upon the filing of an appeal. Yet, at page 2 of the Advisory Action, the Examiner provides substantive comments regarding the limitation of claim 33 added to claim 1.

A second Amendment Under 37 C.F.R. 1.116 is submitted herewith to cancel claim 27, which is duplicative of limitations in base claim 20. Entry of this amendment therefore reduces issues on appeal, whereby entry is believed to be in order and is requested.

Accordingly, the copy of the claims set forth in the Appendix incorporates the changes set forth in the 116 Amendments. If the Examiner's response to this Brief clearly indicates, with reasoning, that either or both of the Amendments are not entered, Appellants request the opportunity to submit a revised brief reflecting the Examiner's position.

V. SUMMARY OF THE INVENTION

The present invention is directed to methods, devices and test kits for determination of an analyte in a sample using biospecific affinity reactions, which methods, devices and test kits employ a calibrator (specification, page 1, lines 1-7).

More particularly, as defined by claim 1, the invention is directed to a lateral flow method for the determination of an analyte in a sample using biospecific affinity reactions. The method comprises forming a complex in a lateral flow matrix, the complex comprising Reactant I---Analyte'---Reactant*, where Reactant* and Reactant I exhibit biospecific affinity to the analyte, Reactant* is analytically detectable, and Analyte' is the analyte or an analyte-related reactant. The method further comprises subsequently determining a detectable signal constituting a sample value from Reactant* in the complex, and determining the amount of analyte in the sample by comparing the sample value with one or more calibrator values, each of which corresponds to a standard amount of analyte. Before determination of the calibrator value, either (i) calibrator, or (ii) a binder for the calibrator has been bound to a matrix, and when a binder for the calibrator has been bound to the matrix, calibrator is added or calibrator predeposited in the matrix is released for binding with the binder. The matrix is insoluble in the liquid medium in which binding of Reactant* to the calibrator occurs. The calibrator and the analyte exhibit biospecific affinity to Reactant* by equivalent binding sites. One or more calibrator zones CZ comprising calibrator or binder for the calibrator are located in a single process flow stream with Reactant I in a detection zone DZ, and all of the detection zones DZ are downstream of all of the calibrator zones CZ in the lateral flow matrix.

Claims 2-19 and 34-36 further define the method of claim 1. According to claim 2, calibrator has been bound to the matrix before the determination of calibrator value, while

according to claim 3, a binder for the calibrator has been bound to the matrix before the determination of calibrator value.

According to claim 4, the binder for the calibrator is one member of a specific binding pair, and the other member of the specific binding pair is coupled or conjugated to the calibrator.

Claim 6 recites that (i) each calibrator zone comprises calibrator in an amount corresponding to a standard amount of analyte, or (ii) each calibrator zone contains calibrator binder, the amount of calibrator binder and the amount of calibrator corresponding to a standard amount of analyte, and Reactant* is bound to the calibrator by transporting Reactant* through the calibrator zones.

According to claim 11, along a single matrix is the flow matrix, and along a single process flow stream, there are one or more calibrator zones (CZ), each of which exhibits a matrix calibrator or a matrix calibrator binder; one or more detection zones (DZ), in which a Capturer is firmly anchored and is either Reactant I or a biospecific affinity reactant, which directly or indirectly binds Reactant I biospecifically; an application zone for Reactant*, $A_{R*}Z$, which is located upstream of said CZ and DZ and to which Reactant* is optionally predeposited; and an application zone for sample (A_SZ). The sample application zone is located upstream of or coinciding with a detection zone, downstream or upstream of or coinciding with $A_{R*}Z$ ($A_SZ/A_{R*}Z$), or upstream of, downstream of or coinciding with a calibrator zone. Additionally, Reactant* is added to $A_{R*}Z$ if Reactant* is not predeposited, or buffer is added to $A_{R*}Z$ if Reactant* is predeposited, and sample is added to A_SZ, optionally premixed with Reactant* if A_SZ and $A_{R*}Z$ coincide, such that analyte and Reactant* reach DZ at the same time, or such that analyte reaches DZ before Reactant*.

Claims 12-15 depend from claim 11. According to claim 12, the calibrator zone or zones CZ comprise a calibrator binder, and calibrator is predeposited upstream of the

calibrator zone or zones. According to claim 13, the process flow stream comprises two or more of said calibrator zones. According to claim 14, the process flow stream comprises one or two of said calibrator zones, and the level of analyte in the sample is obtained by a) comparing a calibrator value from one of the calibrator zones located in the process flow stream including the detection zone, with one or more separately obtained calibrator values to determine a deviation between the measured calibrator value and the separately obtained calibrator values, and b) adjusting the sample value from the detection zone by the deviation, and subsequently obtaining the level of analyte in the sample by comparing the adjusted sample value with one or more of the separately obtained calibrator values.

According to claim 15, A_SZ is (i) common to $A_{R*}Z$, forming a common zone $A_SZ/A_{R*}Z$, or (ii) is located upstream of $A_{R*}Z$, and for alternative (i) sample is premixed with Reactant* before it is added to the common zone $A_SZ/A_{R*}Z$, or sample is added to the common zone $A_SZ/A_{R*}Z$ containing predeposited Reactant*, or for alternative (ii), sample is added to A_SZ, which is located upstream of $A_{R*}Z$ which in turn comprises predeposited Reactant*.

Claim 16 depends from claim 6 and recites that Reactant* has particles as an analytically detectable group, and/or calibrator or calibrator binder is/are anchored to the matrix by particles.

According to claim 17, the analyte is an antibody directed to Reactant I or to Reactant*. Additionally, Reactant* is an antibody directed to the analyte and Reactant I is an antigen or hapten, when the analyte is an antibody directed to Reactant I, or Reactant* is an antigen or a hapten and Reactant I is an antibody directed to the analyte, when the analyte is an antibody directed to Reactant*.

According to claim 18, the analyte is an antigen, and Reactant* and Reactant I are antibodies directed to the analyte. According to clam 19, the method is performed as a part of diagnosing allergy or autoimmune disease.

Claims 34-36 further define Reactant* as comprising a fluorophore group or a chromogenic group (claim 34), metal particles or nonmetal particles (claim 35), and gold sol particles (claim 36).

As defined by claim 20, the invention is directed to a device for transforming measured signal values of a complexed, analytically detectable reactant (Reactant*) to real amounts of analyte in a sample, in connection with performing an analysis method using biospecific affinity reactions for the determination of the amount of analyte in a sample, to form complexes comprising Reactant* in an amount which is related to the amount of analyte in the sample. The device comprises a flow matrix in which there is an area of process flow for the transport of Reactant*. In the process flow area are (i) one or more calibrator zones (CZ) comprising a calibrator, or binder for the calibrator, which is firmly anchored to the matrix, the amounts of calibrator or calibrator binder, respectively, being different for at least two calibrator zones when at least two calibrator zones are present, and the calibrator exhibiting binding sites to which Reactant* binds, when Reactant* is transported through a calibrator zone, (ii) an application zone for Reactant* ($A_{R*}Z$) upstream of the calibrator zones, and (iii) one or more detection zones (DZ). All of the detection zones are downstream of all of the calibrator zones.

Claims 21-26, 28 and 37-39 further define the device of claim 20. Claim 21 recites that a calibrator binder is firmly anchored in the matrix and the device comprises calibrator predeposited upstream of the calibrator zone. Claim 22 recites that the device comprises Reactant* predeposited in $A_{R*}Z$.

According to claim 23, the process flow comprises a detection zone (DZ) which is located downstream of $A_{R*}Z$ and comprises a firmly anchored Capturer to which Reactant* can bind in the DZ, and a zone of application of sample (A_SZ) which is located upstream of or coincides with said DZ. Claims 24-26 and 28 depend from claim 23 and further recite that $A_{R*}Z$ is located upstream of or downstream of or coincides with A_SZ (claim 24), the firmly anchored reactant (Capturer) has biospecific affinity to the analyte or to an analyte-related reactant (claim 25), the firmly anchored reactant (Capturer) has biospecific affinity to a second reactant which in turn has biospecific affinity to the analyte or to an analyte-related reactant (claim 26), and A_SZ is located upstream of all calibrator zones (claim 28).

Claims 37-39 further define Reactant* as comprising a fluorophore group or a chromogenic group (claim 37), metal particles or nonmetal particles (claim 38), and gold sol particles (claim 39).

Finally, claims 29-32 are directed to a test kit comprising a device according to claim 20. According to claim 30, the kit comprises Reactant*, while according to claim 31, the kit comprises calibrator when the device has the calibrator binder bound to the matrix. According to claim 32, Reactant* has biospecific affinity to analyte or an analyte-related reactant and to the calibrator.

VI. ISSUES ON APPEAL

The following issues are on appeal for consideration by the Board:

A. The rejection of claims 1-3, 6, 11-18, 20-25, 28-32 and 34-39 under 35 U.S.C. §103(a) as being unpatentable over the Rylatt et al PCT application WO 97/09620 in view of the Van Deusen et al U.S. Patent No. 5,132,097.

B. The rejection of claim 19 under 35 U.S.C. §103(a) as being unpatentable over Rylatt et al and Van Deusen et al in view of the Self U.S. Patent No. 4,446,231.

C. The rejection of claims 4 and 26 under 35 U.S.C. §103(a) as being unpatentable over Rylatt et al and Van Deusen et al in view of the Weng et al U.S. Patent No. 4,740,468.

VII. GROUPING OF THE CLAIMS

A. With respect to the above-noted issue A on appeal, Appellants submit that claims 2, 6, 13, 14 and 34-39 are independently patentable from claim 1 or claim 20 from which they respectively depend; Appellants concede that claims 3, 11, 12, 15-18, 21-25 and 28-32 stand or fall together with claims 1 and 20, from which they respectively depend.

B. Issue B relates to the single claim 19.

C. With respect to the above-noted issue C on appeal, Appellants submit that claims 4 and 26 are independently patentable.

Reasons in support of the independent patentability of the respective claims are set forth below.

VIII. ARGUMENTS

As will be set forth in detail below, Appellants submit that the methods, devices and test kits according to the present invention are nonobvious over and patentably distinguishable from the cited combination of Rylatt et al and Van Deusen et al, even in further view of Self or Weng et al. Accordingly, the rejections under 35 U.S.C. §103(a) should be reversed. Favorable action by the Board is respectfully requested.

A. Rylatt et al and Van Deusen et al

The methods, devices and test kits defined by claims 1-3, 6, 11-18, 20-25, 28-32 and 34-39 are nonobvious over and patentably distinguishable from the combination of Rylatt et

al and Van Deusen et al, whereby the rejection of these claims under 35 U.S.C. §103(a) should be reversed.

1. The Examiner's Position

In rejecting claims 1-3, 6, 11-18, 20-25 and 28-39 under 35 U.S.C. §103 as being obvious and unpatentable over Rylatt et al in view of Van Deusen et al, the Examiner asserted that Rylatt et al disclose a lateral flow permeable medium comprising a calibration zone and a test/detection zone wherein the test/detection zone is downstream of the calibration zone. The Examiner referred to Figures 2, 5 and 8. The Examiner acknowledged that Rylatt et al fail to teach that the calibrator and the analyte biospecifically bind to Reactant* by equivalent binding sites. However, the Examiner relied on Van Deusen et al as disclosing a test strip with a standard area/calibration zone and a test area/detection zone wherein a labeled reagent binds to both calibrator and analyte. The Examiner specifically asserted that claim 20 only recites one calibration zone and one detection zone downstream of the one calibration zone.

2. The Claimed Invention

As defined by claim 1, the invention is directed to a lateral flow method for the determination of an analyte in a sample using biospecific affinity reactions. The method comprises forming a complex in a lateral flow matrix, the complex comprising Reactant I---Analyte'---Reactant*, where Reactant* and Reactant I exhibit biospecific affinity to the analyte, Reactant* is analytically detectable, and Analyte' is the analyte or an analyte-related reactant. The method further comprises subsequently determining a detectable signal constituting a sample value from Reactant* in the complex, and determining the amount of analyte in the sample by comparing the sample value with one or more calibrator values, each of which corresponds to a standard amount of analyte. Before determination of the calibrator value, either (i) calibrator, or (ii) a binder for the calibrator has been bound to a matrix, and

when a binder for the calibrator has been bound to the matrix, calibrator is added or calibrator predeposited in the matrix is released for binding with the binder. The matrix is insoluble in the liquid medium in which binding of Reactant* to the calibrator occurs. The calibrator and the analyte exhibit biospecific affinity to Reactant* by equivalent binding sites. One or more calibrator zones CZ comprising calibrator or binder for the calibrator are located in a single process flow stream with Reactant I in a detection zone DZ, and all of the detection zones DZ are downstream of all of the calibrator zones CZ in the lateral flow matrix.

As defined by claim 20, the invention is directed to a device for transforming measured signal values of a complexed, analytically detectable reactant (Reactant*) to real amounts of analyte in a sample, in connection with performing an analysis method using biospecific affinity reactions for the determination of the amount of analyte in a sample, to form complexes comprising Reactant* in an amount which is related to the amount of analyte in the sample. The device comprises a flow matrix in which there is an area of process flow for the transport of Reactant*. In the process flow area are (i) one or more calibrator zones (CZ) comprising a calibrator, or binder for the calibrator, which is firmly anchored to the matrix, the amounts of calibrator or calibrator binder, respectively, being different for at least two calibrator zones when at least two calibrator zones are present, and the calibrator exhibiting binding sites to which Reactant* binds, when Reactant* is transported through a calibrator zone, (ii) an application zone for Reactant* ($A_{R*}Z$) upstream of the calibrator zones, and (iii) one or more detection zones (DZ). All of the detection zones are downstream of all of the calibrator zones.

The methods and devices according to the present invention provide improvements in analyte determinations employing calibrators. Particularly, the present methods avoid calibration inaccuracies which often occur owing to differences that may exist between calibrator and sample solutions, between runs performed at different times and/or different

places, and between different analytically detectable reactants. These advantages are obtained by the defined methods of claim 1, employing Reactant* which binds to either analyte or calibrator, and forming the complex in the flow matrix, particularly wherein the calibrator zone or zones are located in the same process flow as the detection zone for measuring analyte. Similarly, these advantages are obtained by the defined methods and devices of claims 1 and 20, employing one or more calibrator zones and one or more detection zones, with *all* of the detection zones being downstream of *all* of the calibrator zones. Further, according to claim 20, the calibrator exhibits binding sites to which Reactant* binds when Reactant* is transported through a calibrator zone, and an application zone for Reactant* is upstream of the calibrator zones.

3. The Claims are Nonobvious over the Cited Combination

Rylatt et al disclose a method and device for determination of an analyte in a sample. With reference to Fig. 2 cited by the Examiner, the Rylatt et al device includes a test zone 204 arranged between calibration zones 210 and 211. Thus, *all* of the detection or test zones are not downstream of *all* of the calibration zones as required by claims 1 and 20, but interspersed therein. Moreover, Appellants find no teaching or suggestion by Rylatt et al of a method or device employing Reactant* as presently claimed, binding to both calibrator and analyte as recited in claim 1. Rather, as shown in Fig. 2 of Rylatt et al, the procedure of Rylatt et al employs an analyte detection agent 208 for binding in the test zone and a separate calibration agent 209 for binding in the calibration zone. Further, the procedure described in Fig. 2 of Rylatt et al employs a separate support element for diffusibly attaching the analyte detection agent 208 and the calibration agent 209, and Appellants find no teaching or suggestion by Rylatt et al as to where such elements would be provided in the flow matrix 207.

The Examiner has asserted that claim 20 only requires the presence of one calibration zone and one detection zone and that Rylatt et al clearly teach one calibration zone and one detection zone downstream of the one calibration zone. However, the Examiner's rationale ignores the express limitations of claims 1 and 20, namely, that *all of the detection zones DZ are downstream of all of the calibrator zones CZ in the lateral flow matrix.* Thus, according to claims 1 and 20, if more than one calibrator zone is employed, all of the detection zones DZ are downstream of all of the calibrator zones CZ in the lateral flow matrix. To the contrary, Rylatt et al do not teach all of the detection zones downstream of all of the calibrator zones, as test zone 204 is arranged between calibration zones 210 and 211. Thus, Rylatt et al expressly teach away from the presently claimed methods and devices. It is error to find obviousness where references diverge from and teach away from the invention at hand, *In re Fine*, 5 U.S.P.Q. 2d 1596, 1599 (Fed. Cir. 1988). Thus, it is error to find obviousness of the presently claimed methods and devices based on Rylatt et al.

The Examiner has relied on Van Deusen et al to resolve the deficiencies of Rylatt et al. Van Deusen et al disclose a test strip including a standard or control area 16 containing a known amount of Reactant B (analyte) bound to Reactant A. The test strip is adapted for placement in a test solution containing a test sample (column 4, lines 22-25) and, subsequently, in a solution containing an identifier, for example, bound to a microbead (column 4, lines 34-38). Van Deusen et al provide no teaching or suggestion relating to a lateral flow method or device or for improving reliable calibration in lateral flow techniques. Rather, Van Deusen et al teach solution immersion techniques. While the present methods and devices enable calibration and analyte detection in a single step, the Van Deusen et al method requires at least two immersion steps.

Further, Appellants find no teaching or suggestion by Van Deusen et al for replacing the distinct labeled calibration agent/calibration agent receptor binding pair of Rylatt et al

with a calibrator as presently claimed, which together with analyte exhibits biospecific affinity to Reactant* by equivalent binding sites. Only in hindsight of the presently claimed methods would one of ordinary skill in the art be motivated to combine the teachings of Van Deusen et al, which are more specifically directed to the use of a laser for detecting a light pattern through a reactive surface, with the lateral flow method and apparatus of Rylatt et al in order to obtain the advantage of avoiding process variations between testing and calibration according to the present methods and devices.

Moreover, if the teachings of Van Deusen et al are combined with Rylatt et al as asserted by the Examiner, such a combination does not result in either the method of claim 1 or the device of claim 20. That is, neither Rylatt et al nor Van Deusen et al teach a lateral flow matrix method wherein a single analytically detectable reactant may be employed for both analyte measurement and calibration, as in claim 1. Moreover, neither Rylatt et al nor Van Deusen et al teach a lateral flow method or device employing a lateral flow matrix wherein all detection zones are downstream of all calibration zones, as presently claimed.

In reply to Appellants' previous arguments that Van Deusen et al and Rylatt et al are not properly combinable, the Examiner asserts that because Van Deusen et al show the use of their labeled reagent provides for a standard area and a test area having both calibrator and analyte produced on the same test strip and provide for a method in which it is not necessary for the reactants to come to equilibrium, the asserted combination is proper. However, the Examiner disregards the significant distinctions that the Van Deusen et al test strip is adapted for a two step process comprising placement in a test solution and then subsequent placement in a solution containing identifier, and that Van Deusen et al provide no teaching or suggestion relating to lateral flow techniques or relating to a one step process as taught by Rylatt et al. Those skilled in the art will recognize that lateral flow methodology and devices are not simply interchangeable with solution techniques as described by Van Deusen et al.

Thus, the solution teachings of Van Deusen et al relied upon by the Examiner would not have motivated one of ordinary skill in the art to make the substitutions in the lateral flow matrix teachings of Rylatt et al in the absence of the teachings of the present application and claims.

Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention absent some teaching, suggestion or incentive supporting the combination, *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987). Clearly, that two references relate to the same general technology, in this case calibration, is not sufficient, as the prior art which the Federal Circuit found deficient in *Geiger* all related to water treatment technology. Nevertheless, the Court found that the requisite teaching, suggestion or incentive supporting the combination of prior art was absent. Similarly, in the present rejection, that Rylatt et al and Van Deusen et al each disclose calibration techniques is not sufficient to support their combination along the lines asserted by the Examiner, absent some teaching, suggestion or incentive supporting the combination. Rylatt et al and Van Deusen et al provide no teaching, suggestion or incentive for combining their teachings along the lines of the presently claimed method and device, and particularly provide no teaching or suggestion of all of the limitations of claims 1 and 20, or the advantages taught in the present specification. Thus, Rylatt et al and Van Deusen et al do not render the presently claimed method and device obvious.

Finally, the Examiner fails to explain why Van Deusen et al's teaching of a method in which it is not necessary for the reactants to come to equilibrium provides motivation for modifying the teachings of Rylatt et al. To the contrary, Rylatt et al are particularly concerned with quantitative determinations of analyte amounts in a sample. Thus, the teachings of Van Deusen et al which the Examiner in attempts to use to justify the combination of references simply do not provide the requisite motivation for the combination.

Thus, the methods and devices defined by claims 1-3, 6, 11-18, 20-25, 28-32 and 34-39 are nonobvious over and patentably distinguishable from the combination of Rylatt et al and Van Deusen et al, whereby the rejection under 35 U.S.C. §103 should be reversed.

4. Claim 2 is Independently Patentable

Claim 2 specifies that calibrator has been bound to the matrix before the determination of calibrator value. According to the teachings of Rylatt et al, a calibrator receptor is bound (non-diffusibly attached) to the matrix, and a calibration agent passes through the calibration zone for reaction therewith. Appellants find no teaching or suggestion by Rylatt et al of binding (non-diffusibly attaching) calibrator to the matrix, particularly prior to the determination of a calibrator value.

The deficiencies of Rylatt et al are not resolved by Van Deusen et al. As noted above, Van Deusen et al provide no teaching or suggestion relating to a lateral flow method or device or for improving reliable calibration in lateral flow techniques. Further, Appellants find no teaching or suggestion by Van Deusen et al for replacing calibration agent receptor of Rylatt et al with a calibrator as presently claimed, particularly in a lateral flow matrix.

In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 U.S.P.Q.2d 1481, 1489 (Fed. Cir. 1997). In view of these deficiencies, Rylatt et al and Van Deusen et al do not in combination enable one of ordinary skill in the art to make and use the method of claim 2, and therefore do not render the claimed invention obvious.

Thus, the method defined by claim 2 is nonobvious over and patentably distinguishably from the combination of Rylatt et al and Van Deusen et al, whereby the rejection under 35 U.S.C. §103 should be reversed.

5. Claim 6 is Independently Patentable

Claim 6 recites that (i) each calibrator zone comprises calibrator in an amount corresponding to a standard amount of analyte, or (ii) each calibrator zone contains calibrator binder, the amount of calibrator binder and the amount of calibrator corresponding to a standard amount of analyte, and Reactant* is bound to the calibrator by transporting Reactant* through the calibrator zones. Not only do Rylatt et al fail to teach analyte and calibrator exhibiting biospecific affinity to an analytically detectable reagent (Reactant*) by equivalent binding sites, Rylatt et al provide no teaching or suggestion of a method wherein a single reactant passes through both calibrator zones and detection zones in a flow matrix to provide analytically detectable reactions for both calibration and analyte detection.

Moreover, the deficiencies of Rylatt et al are not resolved by Van Deusen et al. As noted above, Van Deusen et al provide no teaching or suggestion relating to a lateral flow method or device or for improving reliable calibration in lateral flow techniques. Further, Appellants find no teaching or suggestion by Van Deusen et al relating to a method wherein calibration and detection may be conducted in a single step in a flow matrix and Reactant* is bound to calibrator by transporting it through the calibration zone. Rather, Van Deusen et al teach a two step solution method.

In view of these deficiencies, Rylatt et al and Van Deusen et al in combination do not enable one of ordinary skill in the art to make and use the method of claim 6, and therefore do not render the claimed invention obvious, *Motorola, Inc. v. Interdigital Tech. Corp.*, *supra*.

Thus, the method defined by claim 6 is nonobvious over and patentably distinguishably from the combination of Rylatt et al and Van Deusen et al, whereby the rejection under 35 U.S.C. §103 should be reversed.

6. Claim 13 is Independently Patentable

According to claim 13, the process flow stream comprises two or more calibrator zones. As previously noted, claim 1 recites that all of the detection zones DZ are downstream of all of the calibrator zones CZ in the lateral flow matrix.

Contrary to the limitations of claim 13, Rylatt et al teach a flow matrix having two calibration zones, with a test/detection zone therebetween. Rylatt et al clearly teach away from the limitations of claim 13. Moreover, the deficiencies of Rylatt et al are not resolved by Van Deusen et al. As noted above, Van Deusen et al provide no teaching or suggestion relating to a lateral flow method or device, or otherwise relating to positioning of various zones in a lateral flow matrix. Rather, Van Deusen et al teach a two step solution method.

In view of these deficiencies, Rylatt et al and Van Deusen et al in combination do not enable one of ordinary skill in the art to make and use the method of claim 13, and therefore do not render the claimed invention obvious, *Motorola, Inc. v. Interdigital Tech. Corp.*, *supra*.

Thus, the method defined by claim 13 is nonobvious over and patentably distinguishably from the combination of Rylatt et al and Van Deusen et al, whereby the rejection under 35 U.S.C. §103 should be reversed.

7. Claim 14 is Independently Patentable

According to claim 14, the process flow stream comprises one or two of said calibrator zones, and the level of analyte in the sample is obtained by a) comparing a calibrator value from one of the calibrator zones located in the process flow stream including the detection zone, with one or more separately obtained calibrator values to determine a deviation between the measured calibrator value and the separately obtained calibrator values, and b) adjusting the sample value from the detection zone by the deviation, and

subsequently obtaining the level of analyte in the sample by comparing the adjusted sample value with one or more of the separately obtained calibrator values.

Thus, the method of claim 14 allows for correlation between a measured calibrator value and standard calibrator values to account for variations which may be due to real time variables, such as sample temperature, sample viscosity or the like. Appellants find no teaching or suggestion by Rylatt et al or Van Deusen et al regarding such steps or ability.

In view of these deficiencies, Rylatt et al and Van Deusen et al in combination do not enable one of ordinary skill in the art to make and use the method of claim 14, and therefore do not render the claimed invention obvious, *Motorola, Inc. v. Interdigital Tech. Corp.*, *supra*.

Thus, the method defined by claim 14 is nonobvious over and patentably distinguishably from the combination of Rylatt et al and Van Deusen et al, whereby the rejection under 35 U.S.C. §103 should be reversed.

8. Claims 34-39 are Independently Patentable

Claims 34-39 further define Reactant* as comprising a fluorophore group or a chromogenic group (claims 34 and 37), metal particles or nonmetal particles (claims 35 and 38), and gold sol particles (claims 36 and 39).

While Rylatt et al disclose the use of such analytically detectable reactants in their devices, Rylatt et al provide no teaching, suggestion or recognition of the use of a single Reactant* comprising a fluorophore group or a chromogenic group, metal particles or nonmetal particles, or gold sol particles, for detection of an analyte and calibrator in a lateral flow method or device, particularly to which both analyte and calibrator exhibit biospecific affinity to an analytically detectable reagent (Reactant*) by equivalent binding sites.

Moreover, the deficiencies of Rylatt et al are not resolved by Van Deusen et al. As noted above, Van Deusen et al provide no teaching or suggestion relating to a lateral flow

method or device or for improving reliable calibration in lateral flow techniques. Further, Appellants find no teaching or suggestion by Van Deusen et al relating to a method wherein calibration and detection may be conducted in a single step in a flow matrix using Reactant* as recited in the present claims. Rather, Van Deusen et al teach a two step solution method.

In view of these deficiencies, Rylatt et al and Van Deusen et al in combination do not enable one of ordinary skill in the art to make and use the methods or devices of claims 34-39, and therefore do not render the claimed invention obvious, *Motorola, Inc. v. Interdigital Tech. Corp.*, *supra.*

Thus, the methods and devices defined by claims 34-39 are nonobvious over and patentably distinguishably from the combination of Rylatt et al and Van Deusen et al, whereby the rejection under 35 U.S.C. §103 should be reversed.

B. <u>Rylatt et al, Van Deusen et al and Self</u>

The method defined by claim 19 is nonobvious over and patentably distinguishable from the combination of Rylatt et al, Van Deusen et al and Self, whereby the rejection of claim 19 under 35 U.S.C. §103(a) should be reversed.

1. The Examiner's Position

In rejecting claim 19 under 35 U.S.C. §103(a) as being unpatentable over Rylatt et al and Van Deusen et al in view of Self, the Examiner relied on Self as teaching diagnosis of an autoimmune disease.

2. The Claimed Invention

Claim 19 is directed to the method of claim 1, wherein the method is performed as a part of diagnosing allergy or autoimmune disease.

Diagnosing specific allergies or autoimmune diseases, for example IgE antibodies, is often difficult as biological samples such as blood contain a plurality of nonspecific binding members which interfere with reactions necessary for accurate labeling and detection of

specific IgE antibodies. Accordingly, the present method for diagnosing allergy or autoimmune disease is advantageous in that the calibration reactions are conducted upstream of the detection zone(s), thereby reducing interference with the detection zone by the calibrator and/or the calibrator reactant.

3. The Claims are Nonobvious over the Cited Combination

The deficiencies of Rylatt et al and Van Deusen et al with respect to claim 1, on which claim 19 depends, are discussed in detail above, and apply equally as well to claim 19. Moreover, these references provide no teaching or suggestion relating to diagnosis of allergy or autoimmune disease, or the improvement provided by the present method in such diagnosis.

Self does not resolve these deficiencies. That is, Self discloses an immunoassay employing an enzyme label which converts a precursor into a cycling factor, which in turn is interconverted in a cycling detection system. Appellants find no teaching or suggestion by Self relating to a lateral flow method wherein a complex is formed in a lateral flow matrix using Reactant* to which both analyte and calibrator bind as defined in present claim 1, particularly employing one or more calibration zones in the same process flow as a detection zone, with all detection zones downstream of all calibrator zones. Moreover, Appellants find no teaching or suggestion by Self relating to any improvement provided by such methods in diagnosing allergy or autoimmune disease.

In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, *supra*. In view of the failure of Rylatt et al, Van Deusen et al and Self to teach a lateral flow method as claimed, the combination of these references does not enable one of ordinary skill in the art to conduct the method of claim 19 and therefore does not render claim 19 obvious.

Thus, the rejection of claim 19 under 35 U.S.C. §103 based on Rylatt et al, Van Deusen et al and Self should be reversed.

C. Rylatt et al, Van Deusen et al and Weng et al

The method and device defined by claims 4 and 26 are nonobvious over and patentably distinguishable from the combination of Rylatt et al, Van Deusen et al and Weng et al, whereby the rejection of these claims under 35 U.S.C. §103(a) should be reversed.

1. The Examiner's Position

In rejecting claims 4 and 26 under 35 U.S.C. §103(a) as unpatentable over Rylatt et al and Van Deusen et al in view of Weng et al, the Examiner relied on Weng et al as disclosing the use of a specific binding partner that is biospecific to a second binding partner which in turn is specific for an analyte. The Examiner asserted it would have been obvious to incorporate an immobilized specific binding partner as taught by Weng et al in the device of Rylatt et al.

2. The Claimed Invention

According to claim 4, the binder for the calibrator is one member of a specific binding pair, and the other member of the specific binding pair is coupled or conjugated to the calibrator.

According to claim 26, the firmly anchored reactant (Capturer) in the detection zone has biospecific affinity to a second reactant which in turn has biospecific affinity to the analyte or to an analyte-related reactant.

3. The Claims are Nonobvious over the Cited Combination

The deficiencies of Rylatt et al and Van Deusen et al have been discussed above with respect to claim 1 and claim 20, on which claim 4 and claim 26 depend, respectively, and apply equally as well to claims 4 and 26. Moreover, Appellants find no teaching or suggestion by Rylatt et al and Van Deusen et al of the use of a binder for the calibrator, which

is one member of a specific binding pair, and the other member of the specific binding pair is coupled or conjugated to the calibrator, as required by claim 4. Further, Appellants find no teaching or suggestion by Rylatt et al and Van Deusen et al of the use of firmly anchored reactant (Capturer) in the detection zone, to which the Reactant* can bind and which also has biospecific affinity to a second reactant, which in turn has biospecific affinity to the analyte or to an analyte-related reactant, as required by claim 26.

Moreover, these deficiencies are not resolved by Weng et al. That is, Weng et al disclose a method and device for determining the presence of an analyte in a sample suspected of containing the analyte. Appellants find no teaching or suggestion by Weng et al for modifying the device of Rylatt et al in accordance with the method and device as recited in claims 1 and 20, wherein all of the detection or test zones are downstream of the all of the calibration zones, a single Reactant* as presently claimed, binding to both calibrator and analyte, is employed in a lateral flow matrix, and/or where such Reactant* is arranged in the flow matrix. Moreover, Appellants find no teaching or suggestion by Weng et al for replacing the calibrator receptor of Rylatt et al with a binder as recited in claim 4, or replacing the analyte receptor of Rylatt et al with a Capturer as required by claim 26. Thus, Weng et al do not resolve the deficiencies of Rylatt et al and Van Deusen et al.

In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, *supra*. In view of the failure of Rylatt et al, Van Deusen et al and Weng et al to teach a lateral flow method as claimed, the combination of these references does not enable one of ordinary skill in the art to conduct the method of claim 19 and therefore does not render claim 19 obvious. Thus, the rejection of claim 19 under 35 U.S.C. §103 based on Rylatt et al, Van Deusen et al and Weng et al should be reversed.

IV. CONCLUSIONS

Thus, the methods, devices and test kits defined by claims 1-4, 6, 11-26, 28-32 and 34-39 are nonobvious over and patentably distinguishable from the cited combinations of Rylatt et al and Van Deusen et al, Rylatt et al, Van Deusen et al and Self, and Rylatt et al, Van Deusen et al and Weng et al. Accordingly, the rejections under 35 U.S.C. §103(a) should be reversed. Favorable action by the Board is respectfully requested.

Respectfully submitted,

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APPENDIX

1. A lateral flow method for the determination of an analyte in a sample involving utilizing biospecific affinity reactions, and comprising the following steps:

i. forming a complex in a lateral flow matrix, the complex comprising: Reactant I---Analyte'---Reactant*, where

a. Reactant* and Reactant I exhibit biospecific affinity to the analyte,

b. Reactant* is analytically detectable,

c. Analyte' is the analyte or an analyte-related reactant, and subsequently

ii. determining a detectable signal constituting a sample value from Reactant* in the complex, and

iii. determining the amount of analyte in the sample by comparing the sample value with one or more calibrator values, each of which corresponds to a standard amount of analyte,

wherein A) before determination of the calibrator value, either (i) calibrator, or (ii) a binder for the calibrator has been bound to a matrix, and when a binder for the calibrator has been bound to the matrix, calibrator is added or calibrator predeposited in the matrix is released for binding with the binder, and the matrix is insoluble in the liquid medium in which binding of Reactant* to the calibrator occurs, B) the calibrator and the analyte exhibit biospecific affinity to Reactant* by equivalent binding sites, C) one or more calibrator zones CZ comprising calibrator or binder for the calibrator are located in a single process flow stream with Reactant I in a detection zone (DZ), and D) all of the detection zones DZ are downstream of all of the calibrator zones CZ in the lateral flow matrix.

2. The method according to claim 1, wherein calibrator has been bound to the matrix before the determination of calibrator value.

3. The method according to claim 1, wherein a binder for the calibrator has been bound to the matrix before the determination of calibrator value.

4. The method according to claim 1, wherein the binder for the calibrator is one member of a specific binding pair, and the other member of the specific binding pair is coupled or conjugated to the calibrator.

6. The method according to claim 1, wherein

a. (i) each calibrator zone comprises calibrator in an amount corresponding to a standard amount of analyte, or

(ii) each calibrator zone contains calibrator binder, the amount of calibrator binder and the amount of calibrator corresponding to a standard amount of analyte, and

b. Reactant* is bound to the calibrator by transporting Reactant* through the calibrator zones.

11. The method according to claim 1, wherein along a single matrix is the flow matrix, and wherein along a single process flow stream, there are

a. one or more calibrator zones (CZ), each of which exhibits a matrix calibrator or a matrix calibrator binder,

b. one or more detection zones (DZ), in which a Capturer is firmly anchored and is either Reactant I or a biospecific affinity reactant, which directly or indirectly binds Reactant I biospecifically,

c. an application zone for Reactant*, $A_{R*}Z$, which is located upstream of said CZ and DZ and to which Reactant* is optionally predeposited, and

d. an application zone for sample (A_SZ) which is located

i. upstream of or coinciding with a detection zone,

ii. downstream or upstream of or coinciding with $A_{R*}Z$ ($A_SZ/A_{R*}Z$), or

iii. upstream of, downstream of or coinciding with a calibrator zone,

wherein Reactant* is added to $A_{R*}Z$ if Reactant* is not predeposited, or buffer is added to $A_{R*}Z$ if Reactant* is predeposited, and sample is added to A_SZ, optionally premixed with Reactant* if A_SZ and $A_{R*}Z$ coincide, such that analyte and Reactant* reach DZ at the same time, or such that analyte reaches DZ before Reactant*.

12. The method according to claim 11, wherein the calibrator zone or zones CZ comprise a calibrator binder, and calibrator is predeposited upstream of the calibrator zone or zones.

13. The method according to claim 11, wherein the process flow stream comprises two or more of said calibrator zones.

14. The method according to claim 11, wherein the process flow stream comprises one or two of said calibrator zones, and the level of analyte in the sample is obtained by:

a. comparing a calibrator value from one of the calibrator zones located in the process flow stream including the detection zone, with one or more separately obtained calibrator values to determine a deviation between the measured calibrator value and the separately obtained calibrator values, and

b. adjusting the sample value from the detection zone by the deviation, and subsequently obtaining the level of analyte in the sample by comparing the adjusted sample value with one or more of the separately obtained calibrator values.

15. The method according to claim 11, wherein

a. A_SZ is (i) common to $A_{R*}Z$, forming a common zone $A_SZ/A_{R*}Z$ or (ii) is located upstream of $A_{R*}Z$, and

b. for alternative (i) sample is premixed with Reactant* before it is added to the common zone $A_SZ/A_{R*}Z$, or sample is added to the common zone $A_SZ/A_{R*}Z$ containing predeposited Reactant*, or for alternative (ii), sample is added to A_SZ, which is located upstream of $A_{R*}Z$ which in turn comprises predeposited Reactant*.

16. The method according to claim 6, wherein Reactant* has particles as an analytically detectable group, and/or calibrator or calibrator binder is/are anchored to the matrix by particles.

17. The method according to claim 1, wherein the analyte is an antibody directed to Reactant I or to Reactant*, and

a. Reactant* is an antibody directed to the analyte and Reactant I is an antigen or hapten, when the analyte is an antibody directed to Reactant I, or

b. Reactant* is an antigen or a hapten and Reactant I is an antibody directed to the analyte, when the analyte is an antibody directed to Reactant*.

18. The method according to claim 1, wherein the analyte is an antigen, and Reactant* and Reactant I are antibodies directed to the analyte.

19. The method according to claim 1, wherein the method is performed as a part of diagnosing allergy or autoimmune disease.

20. A device for transforming measured signal values of a complexed, analytically detectable reactant (Reactant*) to real amounts of analyte in a sample, in connection with performing an analysis method which utilizes biospecific affinity reactions for the determination of the amount of analyte in a sample, to form complexes comprising Reactant* in an amount which is related to the amount of analyte in the sample, wherein the device comprises:

a flow matrix in which there is an area of process flow for the transport of Reactant*, and wherein there are in said area

i. one or more calibrator zones (CZ) comprising a calibrator, or binder for the calibrator, which is firmly anchored to the matrix, the amounts of calibrator or calibrator binder, respectively, being different for at least two calibrator zones when at least two calibrator zones are present, and the calibrator exhibiting binding sites to which Reactant* binds, when Reactant* is transported through a calibrator zone,

ii. an application zone for Reactant* ($A_{R*}Z$) upstream of said calibrator zones, and

iii. one or more detection zones (DZ), all of the detection zones being downstream of all of the calibrator zones.

21. The device according to claim 20, wherein a calibrator binder is firmly anchored in the matrix and the device comprises calibrator predeposited upstream of the calibrator zone.

22. The device according to claim 20, wherein the device comprises Reactant* predeposited in $A_{R*}Z$.

23. The device according to claim 20, wherein the process flow comprises a detection zone (DZ) which is located downstream of $A_{R*}Z$ and comprises a firmly anchored Capturer to which Reactant* can bind in the DZ, and a zone of application of sample (A_SZ) which is located upstream of or coincides with said DZ.

24. The device according to claim 23, wherein $A_{R*}Z$ is located upstream of or downstream of or coincides with A_SZ.

25. The device according to claim 23, wherein the firmly anchored reactant (Capturer) has biospecific affinity to the analyte or to an analyte-related reactant.

26. The device according to claim 23, wherein the firmly anchored reactant (Capturer) has biospecific affinity to a second reactant which in turn has biospecific affinity to the analyte or to an analyte-related reactant.

28. The device according to claim 23, wherein A_SZ is located upstream of all calibrator zones.

29. A test kit, comprising a device according to claim 20.

30. The kit according to claim 29, wherein the kit comprises Reactant*.

31. The kit according to claim 29, wherein the kit comprises calibrator when said device has the calibrator binder bound to the matrix.

32. The device according to claim 20, wherein Reactant* has biospecific affinity to analyte or an analyte-related reactant and to the calibrator.

34. The method according to claim 1, wherein Reactant* comprises a fluorophore group or a chromogenic group.

35. The method according to claim 1, wherein Reactant* comprises metal particles or nonmetal particles.

36. The method according to claim 1, wherein Reactant* comprises gold sol particles.

37. The device according to claim 20, wherein Reactant* comprises a fluorophore group or a chromogenic group.

38. The device according to claim 20, wherein Reactant* comprises metal particles or nonmetal particles.

39. The device according to claim 20, wherein Reactant* comprises gold sol particles.

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